CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40199

CORRESPONDENCE

ANDA 40-199

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

AUG 19 1996

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our telephone conversation of August 6, 1996, and your correspondence received August 9, 1996.

NAME OF DRUG: Oxycodone and Acetaminophen Capsules USP, 5 mg/500 mg

DATE OF APPLICATION: July 9. 1996

DATE OF RECEIPT: July 10, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

/S/ 8/19/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-199
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB. /S/ 8/19/96 date
HFD-615/HGreenberg, CSO /S/ 8/19/96 date
HFD-649/JSimmons, Sup. Chem. _____ date
WP File x:\new\firmsam\Amide\ltrs&rev\40199ack.f
F/T hrw 8-16-96
ANDA Acknowledgement Letter!

1.1

ANDA 40-199

Amid Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls NJ 07424

OCT 31 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Oxycodone and Acetaminophen Capsules USP, 5 mg/500 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

March 9, 1998

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD 630
Metropark North II
7500 Standish Place,
Rockville, MD 20855

ORIG AMENDMENT

MAJOR AMENDMENT

RE: Oxycodone & Acetaminophen Capsules 5 mg/500 mg
ANDA 40-199

Dear Dr. Holcombe:

In reference to the facsimile deficiency letter dated March 3, 1997, regarding our ANDA 40-199, Oxycodone & Acetaminophen Capsules 5 mg/500 mg, please find our response to each observation as follows:

Chemistry Deficiencies:

1. **Regarding composition and components:**
   a) Please include the components of imprinting ink in your component and composition statement.
   b) Please include the components of Gelatin capsules in your component and composition statement.
   c) The color additive used in your product (imprinting ink and gelatin capsules) shall conform with the requirements of 21 CFR. Please also submit FDA color certificate statement for all colors used in capsules that meet 21 CFR color requirements:
   d) Please revise and resubmit your components and composition statement to indicate the correct dosage form.
   e) Please revise Oxycodone HCl amount from mg in your components and composition statement.
   f) Please justify proposed % excess Oxycodone Hydrochloride in your formulation with supporting data.

   Response: Enclosed find revised Component and Composition statement for Oxycodone and Acetaminophen Capsules revised as requested (Attachment I).

RECEIVED
MAR 10 1998
GENERIC DRUGS

The overage for Oxycodone Hydrochloride in this product is based on the moisture content of the active raw material. The formulation and Component and Composition page is revised to include overage based on moisture content and the quantity would be adjusted with excipient lactose. Enclosed find copies of the revised manufacturing batch records (Attachment II).

2. Regarding drug substance:

a) Assay specification in USP for Oxycodone HCl is %. Your assay specification and limit is %. Please clarify and submit revised specifications.

b) Please request and resubmit updated COA from complying with USP 23. Also, please include Individual and total degradation products/related substances limits.

Response: The specification and method for Oxycodone Hydrochloride has been revised to conform to the USP specification of % (Attachment III).

The revised COA specification from is attached which complies with USP 23. Also, it includes individual and total degradation products/related substances limits (Attachment IV).

3. Regarding manufacturing and Processing:

a) Please submit revised master batch records identifying the rate of the capsule filling machine.

Response: The batch records are revised to include rate of filling capsules. This is determined by the speed of the encapsulation machine. (Attachment II)

b) The intended production batch size should be clarified. Please revise your blank batch records accordingly and resubmit.

Response: The intended batch sizes are and capsules. The batch records for these intended batches have been revised. Copies of these intended batch sizes are attached (Attachment II).

c) Your in-process individual lower and upper alert (±8) and action limits (± 10) are wider than average finished product fill weight limits (± 3.5). Please tighten or justify. Please revise your batch records and resubmit.

Response: The specification for the in-process weight ranges for average of ten capsule weight is lower and upper alert (±3.5). However there is always an intra-capsule variation which is greater than average capsule weight variation of (±3.5). Therefore we have set a wider weight variation limit for individual capsules.

We will review the ranges after we have manufactured the production and validation batches. If after the production of these batches the data indicates a tighter range is required then we will tighten the ranges at that time.

d) Please provide your actual yield results for packaging.

Response: The yield for packaging for the submission batch is calculated in the packaging section of the batch record. Results for the yield are attached on p. 309 and 315 of the ANDA for the 1000 and 100 package sizes. The packaging yields for 1000 and 100 package sizes are as follows:

1000's	Control # 6069A1	%yield	%
100's	Control # 6069A2	%yield	%

e. Packaging and labeling records, percent reconciliation and yield limits for packaging and labeling should be included in your batch records.

Response: The packaging and labeling batch record are separate part of the batch record. Amide's products are currently sold in the market under private label and there may be numerous sub-lots from the batch. Controlling these sub-lots under one batch record would be confusing. Therefore, the packaging and labeling batch records are issued and maintained separately from the production batch record. The percent yield for the packaging and labeling section of the batch record is calculated in their respective section.

g) In your batch records the encapsulation stage percent yield is given as % and %. Please comment.

Response: The percent yield for this batch when calculated based on bulk capsules weight is %. This is the yield for capsule stage only and does not include losses at the blending stage. However when the calculation for final capsules is performed based on actual capsule count the percent yield was calculated as %. This yield is the actual yield based on theoretical batch size.

h) Please provide the packaging percent yield limit.

Response: The packaging percent yield limits are
The packaging batch record for this product has been revised to include the percent yield limits. (Attachment V)

i) Labeling reconciliation and yield limits should included in your batch records.

Response: The labeling batch record includes the labeling reconciliation and yield limit. The yield limits are %.

j) The product reconciliation limit is % for executed batches and % for the future production. Please justify the upper limit of %.

Response: In production there is always a possibility of weight variation between individual capsules and occasionally this may account for a gain in number of units produced. The upper limit of % is set to account for the weight variation during production.

4. Regarding container / closures:

a) Please submit removal and application torque specifications and test results for 150cc and 1500cc HDPE finished container closure systems.

Response: Enclosed find the results for the removal and application torque during filling operation for the 150 and 1500 cc HDPE bottle. (Attachment VI)

b) Please submit USP <671> test results for 150cc and 1500cc container / closure systems for

b) Please submit USP <671> test results for 150cc and 1500cc container / closure systems for bottles manufactured with and resins.

Response: Enclosed find test results for the USP test for the 150 and 1500 cc HDPE bottle. (Attachment VII)

c) Please submit your USP <661> test results for 150cc, and 1500cc bottles.

Response: Enclosed find test results for the USP test for the 150 and 1500 cc HDPE bottle (Attachment VII)

d) Please update your COA for to conform with USP 23 requirements and include dye , fiber length and absorbency.

Response: Enclosed find updated COA for (Attachment VIII).

e) Please provide letter of authorization to reference DMF's

Response: are the product codes used by The DMF number for is Enclosed find letter of authorization to reference DMF's (Attachment IX)

5. Regarding laboratory controls:

a) Please indicate the type of action to be taken if the filled capsule weight does not meet the tolerance Specifications.

Response: When the filled capsules weight does not meet the tolerance specification following action is taken:

If any capsule falls outside of % but between %, then weigh additional 10 capsules and pass if all are within %.

If any capsules is within %. Determine the fill weight of those capsules exceeding the limit. Pass if the net contents are between %.

If the net contents of any capsules are outside of %, place the stock on hold to the last QA overcheck and inform Production and Quality Assurance Management. Reject the portion of batch to previous testing, if any capsules are outside of %.

b) Total and individual degradation product limits, related substances / impurity limits and brittleness testing with limit should be included in your COA.

Response: The COA is revised to include total and individual degradation product limits, related substances / impurity limits. Enclosed find the revised copy of the COA. (Attachment X)

The brittleness test is not included in the COA because the accelerated and room temperature stability samples did not show any cracking of capsules which indicate that the formulation has no untoward effect on the brittleness of the capsules. Therefore we feel that this test is not required for this product.

6. Regarding impurities:

a) Please provide the identity of any related substance and degradation products for drug substances, finished Product and reference standard.

Response: Enclosed find revised finished product specification and method (Attachment XI) and reference standard specification and method. (Attachment III).

b) Both accelerated and room temperature data are provided in Method Validation Section (Vol. 1.2, pages 479-539). Please submit the chromatograms of related substances and degradation products for the Drug substance and finished dosage form showing the identity of each peak.

Response: Enclosed find copies of the method validation report for the study of the degradation/impurity study. (Attachment XII)

c) Please provide detection limits and retention times of degradation products.

Response: Enclosed find copy of the method validation report for the limit of detection of the degradation/ impurity study. (Attachment XII).

d) Please provide system suitability data for dissolution method.

Response: Enclosed find the system suitability data of the dissolution method. (Attachment XIII)

7. **Regarding stability:**

a) Please include moisture content specifications and test results in your stability report forms and resubmit.

Response: Oxycodone and Acetaminophen capsules are manufactured by

b) For the stability indicating study, please submit representative chromatograms for each stress study

Response: Representative chromatograms for the stress studies were included in the original application in the method validation section under selectivity section on pages 479 - 539 of the ANDA.

c) Both accelerated and room temperature stability testing do not include capsule brittleness. Please justify.

Response: The brittleness test is not included in the room temperature and accelerated stability studies based on the reason explained in 5(b).

d) Please revise your stability protocol to include test methods and limits for this specific product.

Response: Enclosed find the revised stability protocol with the requested information (Attachment XIV).

e) Description of the capsules, manufacturing site and drug substance manufacturer should be included in the stability reports.

Response: Amide has only one manufacturing site and we only use one drug substance manufacturer, therefore the need to list them is not required. Description of the capsule is included in the stability report as a part of the appearance test which is included in the stability report.

f) Please revise fill count and container size on page 569 from 100's to 1000's and 150cc to 1500cc.

Response: Page 569 is revised to include the revised fill count (Attachment XV).

g) The related substances, degradation products limit and brittleness test methods and results should be included in your product stability protocol and reports.

Response: The related substances, degradation products limit is included in the stability protocol and report. Enclosed find the revised copies of the protocol and report. The brittleness test is not included in the stability program at this time because of the reasons explained in 5(b) and 7(c). (Attachment XVI).

LABELING DEFICIENCIES:

1. CONTAINER

RESPONSE: Container labels have been revised as recommended. Enclosed find twelve (12) copies of final printed labels.

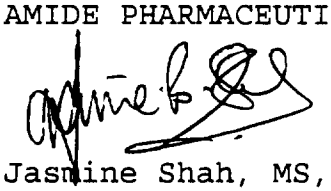
2. INSERTS

RESPONSE: Insert labeling has been revised as recommended. Enclosed find twelve (12) copies of final printed inserts.

Also, enclosed is a side by side comparison of our proposed labeling with the last submission with all differences annotated and explained. (Attachment XVII).

If you or your staff have any question, please feel free to contact us.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.



Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

November 23, 1998

Timothy Ames
Project Manager
Division of Chemistry II
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD 630
Metropark North II
7500 Standish Place,
Rockville, MD 20855

FA

TELEPHONE AMENDMENT

RE: Oxycodone & Acetaminophen Capsules 5 mg/500 mg
ANDA 40-199

Dear Mr. Ames:

In reference to our telephone conversation today, please note that we are withdrawing for the testing of Raw materials form our ANDA application. All testing performed by will be performed by which is also a proposed testing laboratory for this ANDA.

If you or your staff have any question, please feel free to contact us.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
NOV 24 1998
GENERIC DRUGS

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

FA noted to Chemist for review. 10/29/98

October 26, 1998

Timothy Ames
Project Manager
Division of Chemistry II
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD 630
Metropark North II
7500 Standish Place,
Rockville, MD 20855

NDA ... AMENDMENT

N/FA

FACSIMILE AMENDMENT

RE: Oxycodone & Acetaminophen Capsules 5 mg/500 mg
ANDA 40-199

Dear Mr. Ames:

In reference to the facsimile deficiency letter dated October 9, 1998, regarding our ANDA 40-199, Oxycodone & Acetaminophen Capsules 5 mg/500 mg, please find our response to each observation as follows:

Chemistry Deficiencies:

1. Regarding Laboratory Controls:

   a. We could not locate the speed of the encapsulation machine in Attachment II. Please submit the page numbers.

   Response: The speed of the encapsulation machine will be recorded in the batch record. The page numbers in our previous response referencing the machine speed are 032, 048 and 064. Copies of these pages highlighting the speed are attached. (Attachment I)

   b. Please include total related compounds and degradation product limits in your finished product specifications. Resubmit revised drug product specification.

   Response: Finished product specifications are revised to include total related compounds and degradation product limits. Attached is a copy of the finished product specification (Attachment II).

RECEIVED
OCT 27 1998
GENERIC DRUGS

2. **Regarding stability:**

a. Please revise your stability protocol and report to include total impurity limits for this specific product. Please resubmit revised stability protocol testing specifications and reports.

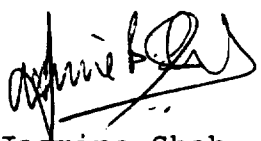
Response: The stability protocol and report is revised as recommended to include total impurity limits. Enclosed find a copy of stability protocol and reports. (Attachment III).

b. There is a typo error in the stability report on page 172 where the stability condition has been identified as 40°C/75% RH for room temperature study. Please correct and resubmit revised page.

Response: Enclosed find a copy of the corrected page 172. (Attachment III)

If you or your staff have any question, please feel free to contact us.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.



Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide Pharmaceutical, Inc.

101 E. Main Street, Little Falls, NJ 07424 • Ph:(201) 890-1440 • Fax:(201) 890-7980

8/5/96

July 9, 1996

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED

JUL 10 1996

GENERIC DRUGS

RE: ANDA - ORIGINAL APPLICATION
OXYCODONE & ACETAMINOPHEN CAPSULES, USP

Dear Mr. Sporn:

Pursuant to section 505 (b) of the Food, Drug and Cosmetic Act and amendments thereto, we are submitting herewith, in duplicate, and Original Abbreviated New Drug Application for the drug, Oxycodone and Acetaminophen Capsules USP.

Included in the file are:

1. All information required by Form 356-H including:

   a) Form 356-H
   b) Archival Copy (blue folder) - 2 Volumes
   c) Review Copy - CMC (red folder) - 2 Volume
   e) Three copies of Analytical Method and Validation Report

2. A copy of CMC Section of the ANDA; the third copy is being to the FDA's Newark District Office, Attn: Regina Brown as required under FDA guidelines.

If you or your staff have any question, please feel free to contact us. Your review of this Abbreviated New Drug Application would be greatly appreciated.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

cc: Regina Brown
FDA, Newark District Office (w/CMC section of ANDA only)